

REMARKS

Claims 35-39 and 70-79 are pending.

The rejection under 35 U.S.C. §102(b)

Claims 35-39 and 70-72 were rejected as being anticipated by WO 99/58478 (Meese).

According to the Office Action, Meese discloses the claimed invention at page 62, third paragraph. See the Office Action, page 3:

Meese et al disclose R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (page 62, 3rd paragraph), (the compound of the instant claim 39). Meese discloses the compound as a free base and provides characterization of the compound in the form of: R_f value and HNMR data. The R_f value indicates that the compound was separated from the impurities on a TLC plate. The isolated compound therefore meets the limitations directed to % purity and salt content. The limitations directed to the therapeutically effective amount is inherently met by the disclosure of Meese et al. The term "therapeutically effective amount" has not been defined in the specification. It is unclear what therapeutic response is required for the amount to be therapeutically effective. Furthermore on pages where a dosing unit is described, specification teaches that the amount of active ingredient will vary based on weight and age of the patient. However the claim fails to specify who the patient is. A therapeutically effective amount for administration to a small mammal might well be far below the dosing units described in the specification.

The Applicants respectfully traverse this rejection.

The third paragraph of page 62 of Meese reads as follows:

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.38 (4) , starting material: 0.26; colourless oil (yield 95%); NMR (CDCl₃): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138.76, 143.93, 147.97, 175.39.

Hydrochloride: colourless hygroscopic solid; [α]_D²⁰ = +5.5 (c = 1.0, chloroform); NMR (CDCl₃) : 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23,

34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40,
128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

The Office Action interprets the first portion of this paragraph as a disclosure of the composition of claim 39, i.e., the free base of fesoterodine, with a salt content of less than 10% by weight, a degree of purity of above 97 percent by weight, and in a therapeutically effective amount. The reasoning behind this interpretation appears to be that, since the second portion of this paragraph is explicitly directed to the hydrochloride salt of fesoterodine, the first portion must be directed to the claimed compound.

See, e.g., the Office Action, page 4:

The reason Examiner is convinced that the data corresponds to the free base of fesoterodine and not to the hydrochloride is because right under the above described data Meese provides the NMR of the hydrochloride, which Meese also labels as "hydrochloride". The two NMRs are carried out in the same deuterated solvent (deuterated chloroform) and display different peaks, which means the compound labeled as hydrochloride is not the same compound as the one labeled R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

The Applicants respectfully submit that this argument can demonstrate, at most, that the substance in the first portion of the third paragraph of page 62 is something other than the hydrochloride salt of fesoterodine. But there is no reason to believe that it is the free base of fesoterodine, with a salt content of less than 10% by weight, a degree of purity of above 97 percent by weight, and in a therapeutically effective amount. It could well be a composition comprising fesoterodine with a salt content of 20% by weight, or 30%, or 40%. Or with a degree of purity of 90% by weight, or 85%, or 80%. Or in an amount well below any possible therapeutically effective amount.

The crucial point is that one cannot know. In view of this uncertainty, an anticipation rejection is not proper. Since Meese does not explicitly disclose that the substance in the first portion of the third paragraph of page 6 meets the claimed limitations, an anticipation rejection here can only be predicated on a finding that those limitations are disclosed inherently. But a finding of inherency is not appropriate in the face of such uncertainty. In fact, a finding of inherency is not appropriate in the face of any uncertainty. It is well settled that to establish inherency, it must be clear that the “missing descriptive matter is necessarily present in the thing described in the reference” (*In re Robertson*, 169 F. 3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999) (underscoring added) and that “in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics *necessarily flows*” [italics in original] from the teachings of the reference (*Ex parte Levy*, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). The fact that a certain result or characteristic may occur or be present is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F. 3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993). The doctrine of inherency is available “only when the prior inherent event can be established as a certainty” (*Ethyl Molded Products Co. v. Petts Package, Inc.*, 9 U.S.P.Q. 2d 1001, 1032 (E.D.Ky. 1988); *See also W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F. 2d 1540, 1554, 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983) and *Ex parte Standish*, 10 U.S.P.Q. 1454, 1457 (Bd. Pat. App. & Int. 1988)).

The Office Action further stated that its interpretation of the third paragraph of page 62 is supported by the disclosure of a method of making the free base of fesoterodine a few pages before page 62. See the Office Action, page 4:

Regarding Meese's disclosure of preparation of the compound, it's true, that procedure for how to prepare the hydrochloride (page 61, titled Salt formation) precedes the spectral data of the compounds prepared. However, on the previous page (page 60) a procedure for preparation of the freebase esters is provided.

Presumably, the Office Action is here referring to the disclosure at page 59, line 24, to page 60, line 15, of Meese, which reads as follows:

Esters of Carboxylic Acids

A stirred solution of (\pm) -2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid mono-chloride for compounds of formula II, 2.50 mmol for compounds of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.

The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

The above-quoted portion of Meese describes a process for the preparation of a class of compounds that includes those presently claimed. But again, there is no explicit disclosure that the products of the disclosed process are free bases with a salt content of less than 10% by weight, a degree of purity of above 97 percent by weight, and in a therapeutically effective amount. Thus, even if the Office Action's assumption that one of the products of this process

was the substance that was analyzed in the first portion of the third paragraph of page 62, this would do nothing to eliminate the uncertainty as to what precisely was the nature of the substance that was analyzed in the first portion of the third paragraph of page 62 in terms of salt content, degree of purity, and amount.

Furthermore, the description of the products of this process ("colourless to light yellow solids or viscous syrups," see page 60, lines 13-14) does not match the description of the substance in the first portion of the third paragraph of page 62 ("colourless oil").

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

The rejection under 35 U.S.C. §103(a)

Claims 35-39 and 70-79 were rejected as being obvious over Meese.

This rejection is premised on the view that the third paragraph of page 62 of Meese discloses the claimed limitations regarding purity and salt content. See the Office Action, page 5:

Meese et al disclose R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (page 62, 3rd paragraph), (the compound of the instant claim 39). Meese discloses the compound as a free base and provides characterization of the compound in the form of: Rf value and HNMR data. The Rf value indicates that the compound was separated from the impurities on a TLC plate. The isolated compound therefore meets the limitations directed to % purity and salt content.

However, as discussed above in connection with the anticipation rejection, the limitations regarding purity and salt content, if they are to be found in Meese, must be found inherently and the evidence of record does not support a finding that Meese inherently

discloses those limitations. Accordingly, the Office Action has not provided an adequate basis for finding these limitations in the prior art and for this reason alone this rejection should be withdrawn.

The Office Action stated that the claimed limitations regarding a therapeutically effective amount, though not disclosed in Meese, could be easily arrived at by preparative scale thin layer chromatography (TLC). See the Office Action, page 6:

One skilled in the art would have found it obvious to prepare enough of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester to formulate it into a dosing unit. Since Meese et al teach preparation of pharmaceutical compositions, it would be obvious to prepare enough active ingredients for a pharmaceutical preparation. Preparing sufficient quantity with the instantly claimed purity is taught by Meese. The R_f value provided by Meese on page 62, corresponds to the compounds separation on thin layer chromatography, which provides one skilled in the art with means to isolate and purify the compound of the Meese on a larger scale. Such purification can [sic, be done?] via Prep scale TLC, both [sic] of which is a commonly utilized procedure that is well known to those skilled in the arts.

Besides again relying inappropriately on inherency,¹ this appeal to a well-known procedure in the art flies in the face of the evidence of record. As explained in the Amendment filed October 6, 2010, pages 11-17, evidence from the present application, the Kanzler Declaration, and Meese itself, all point to the conclusion that Meese, even combined with conventional purification techniques, would not yield a therapeutically effective amount of the free base of the compounds recited in the present claims at the recited salt and purity levels without the need for undue experimentation.

¹ "Preparing sufficient quantity with the instantly claimed purity is taught by Meese. The R_f value provided by Meese on page 62, corresponds to the compounds separation on thin layer chromatography, which provides one skilled in the art with means to isolate and purify the compound of the Meese on a larger scale."

Against this experimental evidence, the Office Action presents only an assumption that preparative TLC would work. Moreover, the Office Action's assumption that preparative TLC would work again relies on the view that the third paragraph of page 62 of Meese inherently discloses the required purity and salt levels. See the Office Action, page 7:

[B]ased on Meese's ability to separate the said compound via thin layer chromatography, one skilled in the art would be [sic] expect that a Prep-TLC technique would be successful in performing the purification. The expectation of success is based on the success of TLC demonstrated by Meese. Since TLC and Prep-TLC are based on the same principle of separation one would expect both to be successful in purification if one of the techniques has been shown to produce a pure product. The R_f value of Meese indicated that TLC is capable of purifying R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester. Based on that showing, one would have reasonable expectation of success in utilizing Prep-TLC for the same purpose.

Of course, the flaw here is that "the success of TLC demonstrated by Meese" has not been demonstrated and thus it is not the case that "one of the techniques has been shown to produce a pure product." The Office Action assumed that the TLC described in Meese achieved the claimed purity (see above quote: "The R_f value of Meese indicated that TLC is capable of purifying R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester." But neither the retardation factor (R_f = the ratio of the distance traveled by the center of a spot to the distance traveled by the solvent front) nor the NMR data reported in Meese are necessarily indicative of the purity of the compound tested. As is understood by those skilled in the art, the determination of the degree of purity of a compound is usually performed using HPLC, not TLC.

Furthermore, as discussed on pages 14-17 of the Amendment filed October 6, 2010, Meese discloses that two compounds with related, but different structures, gave the same R_f value when subjected to TLC in the same solvent system. In other words, Meese's TLC was

incapable of separating these two compounds. The compounds of Formula I of the present claims and their reaction by-products are also compounds with related, but different structures.

The evidence provided by Meese thus indicates that TLC would also be unable to separate compounds of Formula I from their reaction by-products. Given that Meese's TLC was unable to separate closely related compounds, what basis is there to assume that closely related compounds such as the compounds of Formula I from their reaction by-products could be separated upon scaling-up Meese's system to preparative TLC conditions? At the very least, the evidence indicates that separating the compounds of Formula I from their reaction by-products would not be routine but instead would require a great deal, i.e., an undue amount, of experimentation.

Moreover, the Office Action overlooks the fact that those of ordinary skill in the art consider TLC to be primarily an analytical rather than a preparative method. TLC is generally used for such purposes as: monitoring the progress of a reaction, identifying compounds present in a given substance, or determining the purity of a substance. One of ordinary skill in the art, seeking to provide a compound of Formula I as an active pharmaceutical ingredient (API) for use as a drug, and being aware of the TLC spot of Meese, would not be motivated to chose preparative TLC, because preparative TLC is intrinsically very inefficient at providing a pure product in kg scale. For the preparation of 1 kg of API, an impracticably large amount of stationary phase as well as solvent (eluent) in a huge planar chromatographic plate would be required. The band corresponding to the compound of Formula I would have to be scraped off the backing material and the product would then have to be extracted with a suitable solvent and filtered to give the isolated product upon removal of the solvent. Such an approach is simply not practical. The TLC

ratio between silica (stationary phase) and raw product is beyond 1000; this means that for separating 1 kg of fesoterodine free base under preparatory TLC conditions you would need ONE TON of silica. The amount of solvent would be equally immense. Although the present claims require only “a therapeutically effective amount” rather than such gargantuan amounts, one of ordinary skill in the art would understand that the compounds recited in the present claims may be used as therapeutics and thus would be led to choose purification methods that might plausibly be scaled up to very large amounts, since large amounts are used in the large-scale manufacture of therapeutics.

Given the considerations discussed above, there would be no motivation to consider preparatory TLC. A preparatory chemist would first and foremost try column chromatography. As the Kanzler Declaration submitted with the Amendment filed October 6, 2010 shows, this is exactly what the present inventors have done and they have failed, as explained in the Kanzler Declaration.

Assuming, for the sake of argument, that one of ordinary skill in the art **could** have tried to use preparative TLC for trying to provide fesoterodine free base, it is nevertheless not the case that such a person **would** have used preparative TLC because of its intrinsic impracticability and because TLC or preparative TLC does not yield the free base with the required purity. That the prior art could have been modified in a certain way is not enough to support an obviousness rejection. *See, e.g., In re Fritch*, 972 F. 2d 1260, 1266, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): “The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.”

Since the Office Action has not demonstrated that the prior art discloses or suggests the limitations regarding salt content, purity, and amount recited in the present claims, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for March 16, 2011. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response. Please charge any corresponding fees for the Petition to Kenyon & Kenyon LLP's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Director is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

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BY: /Joseph A. Coppola/
Joseph A. Coppola
Reg. No. 38,413
KENYON & KENYON LLP
One Broadway
New York, NY 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)

CUSTOMER NUMBER 26646